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JUL 30 2002
PATENT & TRADEMARK OFFICE
In re Application of:)
Hartmut STROBEL et al.) Group Art Unit: 1614
Serial No.: 10/073,203) Examiner:
Filed: February 13, 2002)
For: ACYLATED 6,7,8,9-)
TETRAHYDRO-5H-)
BENZOCYCLOCHEPTENYL-)
AMINES AND THEIR USE AS)
PHARMACEUTICAL)

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

CLAIM FOR PRIORITY

Under the provisions of 35 U.S.C. § 119, Applicants hereby claim the benefit of the filing date of European Patent Application No. 01102853.7, filed February 13, 2001, for the above-identified U.S. patent application.

In support of this claim for priority, enclosed is one certified copy of the priority application.

Respectfully submitted,

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By: 

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Dated: July 30, 2002

EFC/FPD/gah
Enclosures

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Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

01102853.7

Der Präsident des Europäischen Patentamts;
im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

DEN HAAG, DEN
THE HAGUE, 02/05/02
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Blatt 2 d r Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation

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Application no.: **01102853.7**
Demande n°:

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Anmelder:
Applicant(s):
Demandeur(s):
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Title of the invention:
Titre de l'invention:

Acylated 6,7,8,9-tetrahydro-5H-benzocycloheptenyl amines and their use as pharmaceuticals

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

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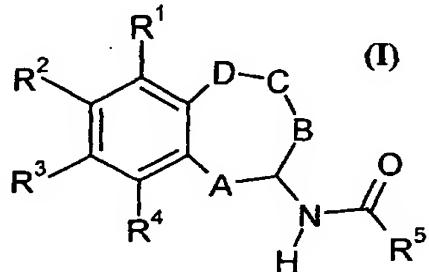
Aventis Pharma Deutschland GmbH

13. Februar 2001
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**Acylated 6,7,8,9-tetrahydro-5H-benzocycloheptenyl amines
and their use as pharmaceutical**

10 The present invention relates to acylated 6,7,8,9-tetrahydro-5H-benzocycloheptenyl amines of the general formula (I) with the definitions of R¹ to R⁵ and A to D given below in the text, and their use as pharmaceutical agents.



15

Endothelial NO synthase (eNOS, NOS-III) belongs to a group of three isoenzymes which produce nitric oxide (NO) by oxidation of arginine. Endothelially released NO is of central importance in a number of key cardiovascular mechanisms. It has a vasodilating effect and inhibits the aggregation of platelets, the adhesion of leukocytes to the endothelium and the 20 proliferation of intimal smooth muscle cells.

Endothelial NO synthase is subject to physiological and pathophysiological regulation both at the transcriptional and at the post-transcriptional level. Enzyme already present in the endothelium may undergo calcium-dependent and calcium-independent activation through 25 phosphorylation of specific amino acids, but also by direct interactions with specific proteins. Stimulators of this, usually transient, NO release are, extracellular arginine, 17 β -estrogen and the mechanical stimulus exerted on the luminal surface of the endothelium by the blood flow (shear stress). The latter additionally leads to regulation of eNOS at the transcriptional level. Thus, for example, Sessa et al. (Circ. Research 74 (1994) 349-353) were able by means of exercise training and the increase in shear stress 30 associated therewith to obtain a marked increase in ecNOS.

Whether regulation at the post-transcriptional level is relevant *in vivo*, is often not unambiguously proved. Thus, for example, administration of a high arginine dose is followed by only a transient improvement in the endothelium-dependent vasorelaxation in patients with coronary heart disease.

5

On the other hand, the significance of the upregulation of the eNOS protein is scientifically accepted. Thus, there are findings which show that the protective properties of the HMG-CoA reductase inhibitor simvastatin can be attributed, besides the lipid lowering, also in part to an increase in eNOS expression *in vivo* (Endres et al., Proc. Natl. Acad. Sci. USA 95 (1998) 8880-8885). It is additionally known that single point mutations in the 10 5'-flanking region of the eNOS gene ("eNOS promoter"), and the reduction in the rate of eNOS gene transcription associated therewith, in the Japanese population is associated with an increase in the risk of coronary spasms (Nakayama et al., Circulation 99 (1999) 2864-2870).

15

The current assumption therefore is that the transcriptional and post-transcriptional mechanisms of eNOS regulation are seriously disturbed in a large number of disorders, especially in cardiovascular disorders. Even in very early stages of a wide variety of cardiovascular disorders it is possible for a dysfunction of this type in the endothelium 20 lining the blood vessels to lead to a deficiency of bioactive NO, which is manifested as the disorder progresses in the form of measurable pathophysiological and morphological changes. Thus, critical steps in early atherogenesis are speeded up by a decrease in endothelial NO release, such as, for example, the oxidation of low density lipoproteins, the recruitment and deposition of monocytes in the intima of vessels, and the proliferation of 25 intimal cells. A consequence of atherogenesis is the formation of plaques on the inside of the blood vessels, which may in turn lead, through a diminution in the shear stress, to a further decrease in endothelial NO release and a further deterioration in the pathology. Since endothelial NO is also a vasodilator, a decrease thereof frequently also leads to hypertension, which may, as an independent risk factor, cause further organ damage.

30

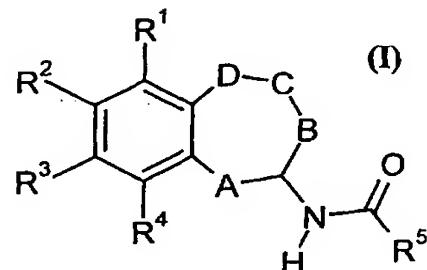
The aim of a therapeutic approach to the treatment of these disorders must accordingly be to interrupt this chain of events by increasing the endothelial NO expression. Gene transfer experiments which lead *in vitro* to overexpression of NO synthase in previously damaged vessels are in fact able to counteract the described processes and are thus evidence of the 35 correctness of this approach (Varenne et al., Hum. Gene Ther. 11 (2000) 1329).

Some low molecular weight compounds which, in cell cultures, may lead to a direct effect on eNOS transcription and expression are disclosed in the literature. The statins which have already been mentioned are, however, the only substances for which it has been possible to date to show such an increase in eNOS in vivo as a side effect. In view of the 5 known range of side effects of this class of substances, however, it is unclear how far this effect is present in a toxicologically unproblematic dose.

Liao et al. claim in WO 99/47153 and WO 00/03746 the use of rhoGTPase inhibitors and 10 agents which influence the organization of the actin cytoskeleton for increasing eNOS in endothelial cells and for the therapy of various disorders such as, for example, strokes or pulmonary hypertension, without, however, indicating a specific way of achieving this.

15 Thus, there exists a strong need for compounds which upregulate eNOS-expression in endothelial cells. The object of the present invention is to provide compounds showing this ability.

This object is attained by acylated 6,7,8,9-tetrahydro-5H-benzocycloheptenyl amines according to the general formula (I) or a pharmaceutically acceptable salt thereof.



20

In the above formula,

R¹ and R⁴ are independently from each other selected from the group consisting of:

H; unsubstituted and at least monosubstituted C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl and C₂-C₁₀-alkynyl, the substituents of which are selected from the group consisting of F, OH, C₁-C₆-alkoxy, (C₁-C₆-alkyl)mercapto, CN, COOR⁶, CONR⁷R⁸, unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃; unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃; R⁹CO; CONR¹⁰R¹¹; COOR¹²; CF₃; halogenes; pseudohalogenes; NR¹³R¹⁴; OR¹⁵; S(O)_mR¹⁶; SO₂NR¹⁷R¹⁸; and NO₂;

R^2 and R^3 are independently from each other selected from the group consisting of:
H; halogenes; pseudohalogens; unsubstituted and at least monosubstituted C_1 - C_6 -alkyl the substituents of which are selected from the group consisting of OH, phenyl, and heteroaryl;
5 OH; C_1 - C_6 -alkoxy; phenoxy; $S(O)_mR^{19}$; CF_3 ; CN; NO_2 ; (C_1 - C_6 -alkyl)amino; di(C_1 - C_6 -alkyl)amino; (C_1 - C_6 -alkyl)-CONH-; unsubstituted and at least monosubstituted phenyl-CONH and phenyl- SO_2 -O-, the substituents of which are selected from the group consisting of halogenes, pseudohalogens, CH_3 and methoxy; (C_1 - C_6 -alkyl) SO_2 -O-; unsubstituted and at least monosubstituted (C_1 - C_6 -alkyl)CO, the substituents of which are selected from the group consisting of F, di(C_1 - C_3 -alkyl)amino, pyrrolidinyl and piperidinyl; and phenyl-CO, the phenyl part of which can be substituted by one or more substituents from the group consisting of C_1 - C_3 -alkyl, halogenes and methoxy;

10 A is selected from the group consisting of CH_2 , $CHOH$ and CH -(C_1 - C_3 -alkyl);
15 B is selected from the group consisting of CH_2 and CH -(C_1 - C_3 -alkyl);

C independently has the same meaning as B;
20 D independently has the same meaning as B;

R^5 is an aryl or a heteroaryl group which can be unsubstituted or carry one or more substituents selected from the group consisting of: halogenes; pseudohalogens; C_1 - C_{10} -alkyl; C_3 - C_5 -alkandiyil; phenyl; phenylsubstituted C_1 - C_4 -alkyl; CF_3 ; OH; C_1 - C_{10} -alkoxy; 25 phenoxy; benzyloxy; CF_3O ; (C_1 - C_{10} -alkyl)COO; $S(O)_mR^{20}$; (C_1 - C_{10} -alkyl)amino; di(C_1 - C_{10} -alkyl)amino; (C_1 - C_{10} -alkyl)-CONH-; (C_1 - C_{10} -alkyl)-CON(C_1 - C_3 -alkyl)-; (C_1 - C_{10} -alkyl)-CO; CF_3 -CO; - OCH_2O -; - OCF_2O -; - OCH_2CH_2O -; - CH_2CH_2O -; phenylamino; phenyl-CO; $COOR^{21}$; $CONR^{22}R^{23}$; $SO_2NR^{24}R^{25}$; and aromatic or aliphatic, mononuclear 5- to 7-membered heterocycles containing 1 to 3 heteroatoms from the group consisting of N, 30 O and S which can be substituted by one or more substituents from the group consisting of halogenes, C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy and CF_3 ; wherein all phenyl groups and phenyl-containing groups which may be present in the said substituents of the said aryl or heteroaryl groups can be substituted by one or more groups selected from halogenes, pseudohalogens, C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy, and CF_3 ;

35 R^6 is H, C_1 - C_6 -alkyl or benzyl;

R^7 is selected from the group consisting of:

H; C_1 - C_6 -alkyl which can be phenyl-substituted; phenyl; indanyl; and heteroaryl; and wherein each of the aforementioned aromatic groups can be unsubstituted or carry one or more substituents from the group consisting of halogenes, pseudohalogenes, C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy and CF_3 ;

R^8 is H or C_1 - C_6 -alkyl;

R^9 is C_1 - C_6 -alkyl which can be unsubstituted or carry one or more substituents from the group consisting of: F; di(C_1 - C_3 -alkyl)amino; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy, halogenes, pseudohalogenes, and CF_3 ;

R^{10} independently has the same meaning as R^7 ;

R^{11} independently has the same meaning as R^8 ;

R^{12} independently has the same meaning as R^6 ;

R^{13} is selected from the group consisting of: H; C_1 - C_6 -alkyl; and unsubstituted and substituted phenyl, benzyl, heteroaryl, phenyl-CO, and heteroaryl-CO, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy, and CF_3 , and wherein one or more of these substituents can be present;

R^{14} is H or C_1 - C_6 -alkyl;

R^{15} is selected from the group consisting of: H; C_1 - C_6 -alkyl; and substituted and unsubstituted benzyl, phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy, and CF_3 , and wherein one or more of these substituents can be present;

R^{16} is selected from the group consisting of: C_1 - C_6 -alkyl; CF_3 ; and substituted and unsubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy, and CF_3 , and wherein one or more of these substituents can be present;

R^{17} independently has the same meaning as R^7 ;

R¹⁸ independently has the same meaning as R⁸;

R¹⁹ independently has the same meaning as R¹⁶;

5

R²⁰ independently has the same meaning as R¹⁶;

R²¹ independently has the same meaning as R⁶;

10 R²² independently has the same meaning as R⁷;

R²³ independently has the same meaning as R⁸;

R²⁴ independently has the same meaning as R⁷;

15

R²⁵ independently has the same meaning as R⁸;

heteroaryl is a 5 to 10-membered, mono- or bicyclic aromatic heterocycle containing one or more heteroatoms from the group consisting of N, O and S;

20

aryl is phenyl, naphth-1-yl or naphth-2-yl;

m is 0, 1 or 2.

25

If, in the compounds of formula (I), groups or substituents such as, for example, aryl, heteroaryl, alkyl etc., can be present several times, they all independently from each other have the meanings indicated and can hence, in each individual case, be identical with or different from each other. One example is the di(C₁-C₁₀-alkyl)amino group in which the alkyl substituents can be identical or different.

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Alkyl, alkenyl and alkynyl residues can be linear or branched, acyclic or cyclic. This also applies when they are part of other groups, for example in alkoxy groups, alkoxy carbonyl groups or amino groups, or when they are substituted.

35

Examples for alkyl groups are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, the n-isomers of these residues, isopropyl, isobutyl, isopentyl, sec-butyl, tert-butyl, neopentyl, 3,3-dimethylbutyl. The term alkyl here also expressly includes

cycloalkyl residues and cycloalkyl-alkyl-residues (alkyl substituted by cycloalkyl) containing at least three carbon atoms. Examples for such cycloalkyl residues are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. All cycloalkyl groups can be substituted by one or more identical or different (C₁-C₄)-alkyl residues, in particular by methyl. Examples for substituted cycloalkyl residues are 4-methylcyclohexyl, 4-tert-butylcyclohexyl or 2,3-dimethylcyclopentyl. Furthermore, unless stated otherwise, the term alkyl here also includes unsubstituted alkyl residues as well as alkyl residues which are substituted by one or more, for example one, two, three or four, identical or different residues, for example aryl groups. In substituted alkyl residues, for example arylalkyl, hydroxyalkyl such as -(C₁-C₃)-alkyl-OH or alkoxyalkyl such as -(C₁-C₃)-alkyl-O-(C₁-C₄)-alkyl, the substituents can be present in any desired position.

Examples for alkenyl and alkynyl groups are the vinyl residue, the 1-propenyl residue, the 2-propenyl residue (allyl residue), the 2-butenyl residue, the 2-methyl-2-propenyl residue, the 3-methyl-2-butenyl residue, the ethynyl residue, the 2-propynyl residue (propargyl residue), the 2-butynyl residue or the 3-butynyl residue. The term alkenyl here also expressly includes cycloalkenyl residues and cycloalkenyl-alkyl-residues (alkyl substituted by cycloalkenyl) containing at least three carbon atoms. Examples for cycloalkenyl residues are cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl. All cycloalkenyl groups can be substituted by one or more identical or different (C₁-C₄)-alkyl residues, in particular by methyl. Furthermore, unless stated otherwise, the term alkenyl and alkynyl here also includes unsubstituted alkenyl and alkynyl residues as well as alkenyl and alkynyl residues which are substituted by one or more, for example one, two, three or four, identical or different residues, for example aryl groups. In substituted alkenyl and alkynyl residues, for example arylalkenyl, hydroxyalkenyl such as -(C₂-C₃)-alkenyl-OH or alkoxyalkenyl such as (C₁-C₃-alkyl)-O-(C₂-C₄-alkenyl)-, the substituents can be present in any desired position.

Examples for C₃-C₅-alkandiyl are -CH₂CH₂CH₂-,-CH₂-CH(CH₃)-,-CH₂CH₂CH₂CH₂- and -CH₂CH₂CH₂CH₂CH₂- groups.

If not stated otherwise, the above-mentioned phenyl residues, naphthyl and indanyl residues and heterocyclic residues can be unsubstituted or can carry one or more, for example one, two, three or four, of the substituents indicated in the above definition which can be in any desired position. If in compounds of the formula (I) nitro groups are present as substituents, in total only up to two nitro groups are preferably present in the molecule. In monosubstituted phenyl residues the substituent can be in the 2-position, the 3-position

or the 4-position, in disubstituted phenyl residues the substituents can be in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In trisubstituted phenyl residues the substituents can be in 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position or 3,4,5-position. In fourfold substituted phenyl residues, the substituents can be in the 2,3,4,5-position, the 2,3,4,6-position, or the 2, 3,5,6-position. 5 Tollyl (= methylphenyl) can be 2-tollyl, 3-tollyl or 4-tollyl. Naphthyl can be 1-naphthyl or 2-naphthyl. In monosubstituted 1-naphthyl residues the substituent can be in the 2-position, the 3-position, the 4-position, the 5-position, the 6-position, the 7-position or the 8-position, in monosubstituted 2-naphthyl residues in the 1-position, the 3-position, the 4-position, the 5-position, the 6-position, the 7-position or the 8-position. In higher 10 substituted naphthyl radicals, for example 1-naphthyl radicals or 2-naphthyl radicals which carry two or three substituents, the substituents can also be situated in all possible positions. Indanyl residues include indan-1-yl residues and indan-2-yl residues which can be unsubstituted or carry one or more of the substituents indicated. In case the indanyl 15 residues are substituted, the substituent or substituents can be in any of the positions possible.

The above definitions as well as the following definitions relating to monovalent residues 20 equally apply to the divalent residues phenylene, naphthylene and heteroarylene. Those divalent residues can be attached to the adjacent groups by any ring carbon atom. In the case of a phenylene residue, these can be in 1,2-position (ortho-phenylene), 1,3-position (meta-phenylene) or 1,4-position (para-phenylene). In the case of a naphthylene residue the free bonds can be in 1,2-position (= 1,2-naphthylene or 1,2-naphthalenediyl) or in 1,3-position, 1,4-position, 1,5-position, 1,6-position, 1,7-position, 1,8-position, 2,3-position, 25 2,6-position or 2,7-position. In the case of 5-membered ring aromatics containing one heteroatom such as, for example, thiophene or furan, the two free bonds can be in 2,3-position, 2,4-position, 2,5-position or 3,4-position. A divalent residue derived from pyridine can be a 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-pyridinediyl residue. In the case of unsymmetrical divalent residues the present invention includes all positional isomers, i. e., 30 in the case of a 2,3-pyridinediyl residue, for example, it includes the compound in which the one adjacent group is present in the 2-position and the other adjacent group is present in the 3-position as well as the compound in which the one adjacent group is present in the 3-position and the other adjacent group is present in the 2-position.

35 Unless stated otherwise, heteroaryl residues, heteroarylene residues, heterocycl residues and rings which are formed by two groups bonded to a nitrogen are preferably derived from heterocycles which contain one, two, three or four heteroatoms which can be

identical or different; more preferably they are derived from heterocycles which contain one, two, or three, in particular one or two, heteroatoms which can be identical or different. Unless stated otherwise, the heterocycles can be monocyclic or polycyclic, for example monocyclic, bicyclic or tricyclic. Preferably they are monocyclic or bicyclic. The rings 5 preferably are 5-membered rings, 6-membered rings or 7-membered rings. Examples of monocyclic and bicyclic heterocyclic systems from which residues occurring in the compounds of the formula (I) can be derived, are pyrrole, furan, thiophene, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, 1,3-dioxole, 1,3-oxazole (= oxazole), 1,2-oxazole (= isoxazole), 1,3-thiazole (= thiazole), 1,2-thiazole (= isothiazole), tetrazole, pyridine, 10 pyridazine, pyrimidine, pyrazine, pyran, thiopyran, 1,4-dioxine, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,2,3-triazine, 1,2,4-triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, azepine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, 1,3-oxazepine, 1,3-thiazepine, indole, benzothiophene, benzofuran, benzothiazole, benzimidazole, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine, 15 thienothiophenes, 1,8-naphthyridine and other naphthyridines, pteridin, or phenothiazine, each of them in saturated form (perhydro form) or in partially unsaturated form (for example in the dihydro form or the tetrahydro form) or in maximally unsaturated form, in case the respective forms are known and stable. Thus, suitable heterocycles also include, for example, the saturated heterocycles pyrrolidine, piperidine, piperazine, morpholine and 20 thiomorpholine. The degree of saturation of heterocyclic groups is indicated in their individual definitions. Unsaturated heterocycles can contain, for example, one, two or three double bonds within the ring system. 5-membered rings and 6-membered rings can in particular also be aromatic.

25 Substituents which may be derived from these heterocycles can be attached via any suitable carbon atom. Residues derived from nitrogen heterocycles can carry a hydrogen atom or a substituent on a ring nitrogen atom, and examples include pyrrole, imidazole, pyrrolidine, morpholine, piperazine residues, etc. Those nitrogen heterocyclic residues can also be attached via a ring nitrogen atom, in particular if the respective heterocyclic 30 residue is bonded to a carbon atom. For example, a thienyl residue can be present as 2-thienyl residue or 3-thienyl residue, a furyl residue as 2-furyl residue or 3-furyl residue, a pyridyl residue as 2-pyridyl residue, 3-pyridyl residue or 4-pyridyl residue, a piperidinyl residue as 1-piperidinyl residue (= piperidino residue), 2-piperidinyl residue, 3-piperidinyl residue or 4-piperidinyl residue, a (thio)morpholinyl residue as 2-(thio)morpholinyl residue, 3-(thio)morpholinyl residue or 4-(thio)morpholinyl residue (= thiomorpholino residue). A residue derived from 1,3-thiazole or imidazole which is attached via a carbon 35 atom can be attached via the 2-position, the 4-position or the 5-position.

In case a heterocyclic groups is substituted, it can carry one or more, for example one, two, three or four, identical or different substituents. Substituents in heterocycles can be present in any desired positions, for example in a 2-thienyl residue or 2-furyl residue in the 3-position and/or in the 4-position and/or in the 5-position, in a 3-thienyl residue or 3-furyl residue in the 2-position and/or in the 4-position and/or in the 5-position, in a 2-pyridyl residue in the 3-position and/or in the 4-position and/or in the 5-position and/or in the 6-position, in a 3-pyridyl residue in the 2-position and/or in the 4-position and/or in the 5-position and/or in the 6-position, in a 4-pyridyl residue in the 2-position and/or in the 3-position and/or in the 5-position and/or in the 6-position. Suitable nitrogen heterocycles can also be present as N-oxides or as quarternary salts containing a counterion which is derived from a pharmaceutically acceptable acid. Pyridyl residues, for example, can be present as pyridine-N-oxides.

15 Halogen is fluorine, chlorine, bromine oder iodine, preferably fluorine or chlorine.

Examples for pseudohalogenes are CN and N₃, a preferred pseudohalogene is CN.

The present invention includes all stereoisomeric forms of the compounds of the formula (I). Centers of asymmetry that are present in the compounds of formula (I) all independently of one another have S configuration or R configuration. The invention includes all possible enantiomers and diastereomers and mixtures of two or more stereoisomers, for example mixtures of enantiomers and/or diastereomers, in all ratios. Thus, compounds according to the present invention which can exist as enantiomers can be present in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. In the case of a cis/trans isomerism the invention includes both the cis form and the trans form as well as mixtures of these forms in all ratios. All these forms are an object of the present invention. The preparation of individual stereoisomers can be carried out, if desired, by separation of a mixture by customary methods, for example by chromatography or crystallization, by the use of stereochemically uniform starting materials for the synthesis or by stereoselective synthesis. Optionally a derivatization can be carried out before a separation of stereoisomers. The separation of a mixture of stereoisomers can be carried out at the stage of the compounds of the formula (I) or at the stage of an intermediate during the synthesis. The present invention also includes all tautomeric forms of the compounds of formula (I).

In case the compounds according to formula (I) contain one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically utilizable salts. Thus, the compounds of the formula (I) which contain acidic groups can be present on these 5 groups and can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the formula (I) which contain one or more 10 basic groups, i.e. groups which can be protonated, can be present and can be used according to the invention in the form of their addition salts with inorganic or organic acids. Examples for suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, 15 benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. If the compounds of the formula (I) simultaneously contain acidic and basic groups in the molecule, the invention 20 also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts according to the formula (I) can be obtained by customary methods which are known to the person skilled in the art like, for example by contacting these with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts. The present invention also includes all salts of the 25 compounds of the formula (I) which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

30 The present invention furthermore includes all solvates of compounds of the formula (I), for example hydrates or adducts with alcohols, active metabolites of the compounds of the formula (II), and also derivatives and prodrugs of the compounds of the formula (I) which contain physiologically tolerable and cleavable groups, for example esters, amides and compounds in which the N-H group depicted in formula (I) is replaced with an N-alkyl group, such as N-methyl, or with an N-acyl group, such as N-acetyl or N-argininyl, 35 including pharmaceutically acceptable salts formed on functional groups present in the N-acyl group.

Preferred compounds of the formula (I) are those compounds in which one or more of the residues contained therein have the meanings given below, with all combinations of preferred substituent definitions being a subject of the present invention. With respect to all 5 preferred compounds of the formula (I) the present invention also includes all stereoisomeric forms and mixtures thereof in all ratios, and their pharmaceutically acceptable salts.

10 In preferred embodiments of the present invention, the substituents R¹ to R⁵, A, B, C and D and the groups aryl and heteroaryl of the formula (I) independently from each other have the following meanings. Hence, one or more of the substituents R¹ to R⁵ and A, B, C and D 15 can have the preferred or particularly preferred meanings given below.

15 R¹ is preferably selected from the group consisting of: H; C₁-C₄-alkyl; C₁-C₄-alkoxy; CF₃; halogenes; pseudohalogenes; (C₁-C₄-alkyl)-S(O)_m-; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃; R¹ is in particular H, halogene or C₁-C₄-alkyl.

20 R² is preferably selected from the group consisting of: H; halogenes; pseudohalogenes; and C₁-C₃-alkyl.

R³ and R⁴ are preferably each H.

25 A is preferably selected from the group consisting of CH₂ and CHO_H; A is in particular CH₂.

30 B, C and D are preferably independently from each other selected from the group consisting of CH₂ and CH-CH₃; in particular B and C are each CH₂ while D is CH₂ or CH-CH₃; more particularly B, C and D are CH₂.

35 R⁵ is preferably selected from the group consisting of: phenyl which is optionally substituted by one or more substituents from the group consisting of halogenes, pseudohalogenes, C₁-C₆-alkyl, CF₃, C₁-C₆-alkoxy, trifluoromethoxy, phenoxy, (C₁-C₃-alkyl)amino-, di(C₁-C₃-alkyl)amino, (C₁-C₄-alkyl)-S(O)_m-, phenylmercapto, phenyl which is optionally substituted by one or more halogenes, and -O-CH₂-O-, -O-CF₂-O-, and -OCH₂-CH₂-O-; unsubstituted and at least mono-halogene-substituted benzodioxolyl and

dihydrobenzofuranyl; naphthyl which is optionally substituted by one or more substituents from the group consisting of halogenes, pseudohalogenes, C_1 - C_6 -alkyl, CF_3 , C_1 - C_6 -alkoxy, trifluoromethoxy, phenoxy, $(C_1$ - C_4 -alkyl)- $S(O)_m$ -, phenylmercapto, $-O-CH_2-O-$, $-O-CF_2-O$, and $-O-CH_2-CH_2-O-$; and unsubstituted and at least monosubstituted heteroaryl the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C_1 - C_6 -alkyl, CF_3 , C_1 - C_6 -alkoxy, trifluoromethoxy, phenoxy, $(C_1$ - C_4 -alkyl)- $S(O)_m$ -, phenylmercapto, phenyl which is optionally substituted by one or more halogenes, and $-O-CH_2-O$, $-O-CF_2-O$, and $-O-CH_2-CH_2-O$; R^5 is in particular selected from the group consisting of: 4-fluorophenyl; 4-chlorophenyl; 4-bromophenyl; 4-(C_1 - C_3 -alkyloxy)-phenyl; 4-trifluoromethoxyphenyl; 2-bromo-4-fluorophenyl; 2-chloro-4-fluorophenyl; 3,4-dimethylphenyl; 2,4-dimethylphenyl; 4-chloro-2-methylphenyl; 2-hydroxy-4-methylphenyl; 2-hydroxy-4-ethoxyphenyl; 2-methoxy-4-methylphenyl; 4-phenoxyphenyl; 3-fluoro-4-methylphenyl; benzo[1,3]dioxol-5-yl; 2,2-difluorobenzo[1,3]dioxol-5-yl; 2,3-dihydrobenzofuran-5-yl; thienyl; halogene-substituted thienyl; 5-acetylthienyl; pyridyl; pyridyl which is substituted by halogene and/or (C_1 - C_3 -alkyl).

Heteroaryl is preferably selected from the group consisting of 5- and 6- membered heterocycles containing one or more heteroatoms from the group consisting of N, O, and S; heteroaryl is in particular selected from the group consisting of furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, pyrazolyl, imidazolyl, pyrazinyl, pyridyl and pyrimidinyl.

Aryl is preferably phenyl.

m is preferably 0 or 2.

Compounds of the formula (I) in which some or all of the above-mentioned groups have the preferred meanings or the particularly preferred meanings defined above are also an object of the present invention.

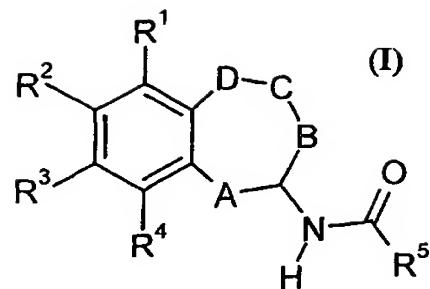
The compounds according to general formula (I) are preferably prepared by acylating the respective 6,7,8,9-tetrahydro-5H-benzocycloheptenyl amine, followed by further functionalization of the thus-obtained compounds. The acylation can be carried out optionally by reaction of the above amines with an acid and a suitable coupling reagent like, for example, carbodiimides, HATU or TOTU in the presence of a base like, for example, diisopropylethyl amine, or by reaction of the above amines with a carboxylic acid chloride employing solvents like, for example, dichloromethane, THF, toluene or dioxane

in the presence of a base like, for example, triethyl amine. The acylation is preferably carried out at room temperature.

5 6,7,8,9-Tetrahydro-5H-benzocycloheptenyl amines employed as educts can be prepared according to methods published in the literature. Appropriate methods have been published in, for example, Vejdelek, Z. J. et al, Collect. Czech. Chem. Commun 39; (1974) 2819; Cannon, J. G et al. J. Med. Chem. 23 (1980) 745; Seidl, G. et al. Chem. Ber. 97 (1964) 249; or Lal, B. et al. J. Med. Chem. 15 (1972) 23.

10 All reactions for the synthesis of the compounds of the formula (I) are per se well-known to the skilled person and can be carried out under standard conditions according to or analogously to procedures described in the literature, for example in Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry), Thieme-Verlag, Stuttgart, or Organic Reactions, John Wiley & Sons, New York. Depending on the 15 circumstances of the individual case, in order to avoid side reactions during the synthesis of a compound of the formula (I), it can be necessary or advantageous to temporarily block functional groups by introducing protective groups and to deprotect them in a later stage of the synthesis, or introduce functional groups in the form of precursor groups which in a later reaction step are converted into the desired functional groups. Such synthesis 20 strategies and protective groups and precursor groups which are suitable in an individual case are known to the skilled person. If desired, the compounds of the formula (I) can be purified by customary purification procedures, for example by recrystallization or chromatography. The starting compounds for the preparation of the compounds of the formula (I) are commercially available or can be prepared according to or analogously to 25 literature procedures. The compounds obtained with the above-identified synthesis methods are a further object of the present invention.

30 The object of the present invention is also attained by 6,7,8,9-tetrahydro-5H-benzocycloheptenyl amines according to the general formula (I), wherein R¹, R², R³, R⁴, R⁵, A, B, C and D have the meaning as defined above, or a pharmaceutically acceptable salt thereof, for use as pharmaceutical.



Compounds of the formula (I) for use as pharmaceutical, in which at least one, preferably all of the above-mentioned groups have the preferred meanings or the particularly preferred meanings defined above are also an object of the present invention.

The compounds according to the general formula (I) can be used to upregulate the expression of the endothelial NO synthase and are helpful pharmaceutical compounds for the treatment of various diseases. In the context of the present invention, treatment includes the therapy as well as the prophylaxis of the respective diseases.

Examples of diseases which can be treated with the compounds according to the present invention include cardiovascular diseases like stable and unstable angina pectoris, coronary heart disease, Prinzmetal angina (spasm), acute coronary syndrome, heart failure, myocardial infarction, stroke, thrombosis, peripheral artery occlusive disease (PAOD), endothelial dysfunction, atherosclerosis, restenosis, endothelial damage after PTCA, hypertension including essential hypertension, pulmonary hypertension, and secondary hypertension (renovascular hypertension, chronic glomerulonephritis), erectile dysfunction, ventricular arrhythmia, and the lowering of cardiovascular risk of postmenopausal women or after intake of contraceptives.

Compounds of the formula (I) can additionally be used in the therapy and prophylaxis of diabetes and diabetes complications (nephropathy, retinopathy), angiogenesis, asthma bronchiale, chronic renal failure, cirrhosis of the liver, osteoporosis, restricted memory performance or a restricted ability to learn.

Preferred indications are stable angina pectoris, coronary heart disease, hypertension, endothelial dysfunction, atherosclerosis and diabetes complications.

The compounds according to the formula (I) can also be used in combination with other pharmaceutically active compounds, preferably compounds which are able to enhance the

effect of the compounds according to the general formula (I). Examples of such compounds include:

statins; ACE-inhibitors; AT1-antagonists; argininase-inhibitors; PDE V-inhibitors; Ca-antagonists; alpha-blockers; beta-blockers; metimazol and analogous compounds; arginine; tetrahydrobiopterin; vitamins, in particular vitamin C and vitamin B6; niacine.

The compounds of the formula (I) and their pharmaceutically acceptable salts, optionally in combination with other pharmaceutically active compounds, can be administered to animals, preferably to mammals, and in particular to humans, as pharmaceuticals by themselves, in mixtures with one another or in the form of pharmaceutical preparations. Further subjects of the present invention therefore also are the compounds of the formula (I) and their pharmaceutically acceptable salts for use as pharmaceuticals, their use as transcription stimulating agent for endothelial NO synthase and in particular their use in the therapy and prophylaxis of the above-mentioned syndromes as well as their use for preparing medicaments for these purposes. Furthermore, subjects of the present invention are pharmaceutical preparations (or pharmaceutical compositions) which comprise an effective dose of at least one compound of the formula (I) and/or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, i.e. one or more pharmaceutically acceptable carrier substances and/or additives.

The pharmaceuticals according to the invention can be administered orally, for example in the form of pills, tablets, lacquered tablets, sugar-coated tablets, granules, hard and soft gelatin capsules, aqueous, alcoholic or oily solutions, syrups, emulsions or suspensions, or rectally, for example in the form of suppositories. Administration can also be carried out parenterally, for example subcutaneously, intramuscularly or intravenously in the form of solutions for injection or infusion. Other suitable administration forms are, for example, percutaneous or topical administration, for example in the form of ointments, tinctures, sprays or transdermal therapeutic systems, or the inhalative administration in the form of nasal sprays or aerosol mixtures, or, for example, microcapsules, implants or rods. The preferred administration form depends, for example, on the disease to be treated and on its severity.

The amount of compounds of the formula (I) and/or its pharmaceutically acceptable salts in the pharmaceutical preparations normally ranges from 0.2 to 800 mg, preferably from 0.5 to 500 mg, in particular from 1 to 200 mg, per dose, but depending on the type of the pharmaceutical preparation it may also be higher. The pharmaceutical preparations usually comprise 0.5 to 90 percent by weight of the compounds of the formula (I) and/or their

pharmaceutically acceptable salts. The preparation of the pharmaceutical preparations can be carried out in a manner known per se. To this end, one or more compounds of the formula (I) and/or their pharmaceutically acceptable salts, together with one or more solid or liquid pharmaceutical carrier substances and/or additives (or auxiliary substances) and, 5 if desired, in combination with other pharmaceutically active compounds having therapeutic or prophylactic action, are brought into a suitable administration form or dosage form which can then be used as a pharmaceutical in human or veterinary medicine.

For the production of pills, tablets, sugar-coated tablets and hard gelatin capsules it is 10 possible to use, for example, lactose, starch, for example maize starch, or starch derivatives, talc, stearic acid or its salts, etc. Carriers for soft gelatin capsules and suppositories are, for example, fats, waxes, semisolid and liquid polyols, natural or hardened oils, etc. Suitable carriers for the preparation of solutions, for example of solutions for injection, or of emulsions or syrups are, for example, water, physiologically 15 sodium chloride solution, alcohols such as ethanol, glycerol, polyols, sucrose, invert sugar, glucose, mannitol, vegetable oils, etc. It is also possible to lyophilize the compounds of the formula (I) and their pharmaceutically acceptable salts and to use the resulting lyophilisates, for example, for preparing preparations for injection or infusion. Suitable carriers for microcapsules, implants or rods are, for example, copolymers of glycolic acid 20 and lactic acid.

Besides the compound or compounds according to the invention and carriers, the pharmaceutical preparations can also contain additives, for example fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, dispersants, preservatives, 25 sweeteners, colorants, flavorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants.

The dosage of the compound of the formula (I) to be administered and/or of a 30 pharmaceutically acceptable salt thereof depends on the individual case and is, as is customary, to be adapted to the individual circumstances to achieve an optimum effect. Thus, it depends on the nature and the severity of the disorder to be treated, and also on the sex, age, weight and individual responsiveness of the human or animal to be treated, on the efficacy and duration of action of the compounds used, on whether the therapy is acute or 35 chronic or prophylactic, or on whether other active compounds are administered in addition to compounds of the formula (I). In general, a daily dose of approximately 0.01 to 100 mg/kg, preferably 0.1 to 10 mg/kg, in particular 0.3 to 5 mg/kg (in each case mg per

kg of bodyweight) is appropriate for administration to an adult weighing approximately 75 kg in order to obtain the desired results. The daily dose can be administered in a single dose or, in particular when larger amounts are administered, be divided into several, for example two, three or four individual doses. In some cases, depending on the individual 5 response, it may be necessary to deviate upwards or downwards from the given daily dose.

The compounds according to the formula (I) can also be used for other purposes than those indicated in the foregoing. Non-limiting examples include diagnostic purposes, the use as biochemical tools, and as intermediates for the preparation of further compounds, e.g. 10 pharmaceutically active compounds.

The present invention will now be illustrated in the following examples:

15 **Examples:**

Preparation of 6,7,8,9-Tetrahydro-5H-benzocyclohepten-6-yl amine

12g (75 mmol) benzosuberone were dissolved in 200 ml methanol at 45°C and 9.66g (82.5 mmol) isoamyl nitrite was added. Subsequently 10 ml concentrated HCl was added 20 dropwise over a period of 10 min. and the mixture was stirred for 3h at 45°C. After concentrating the thus-obtained residue was chromatographically fractionated on silica gel using a methylene chloride-methanol mixture (98:2, v/v) as mobile phase. Yield: 8.5g (60%).

25 8g of the above intermediate were dissolved in 400 ml of glacial acetic acid, 5ml of concentrated sulfuric acid were added and the intermediate was hydrogenated using 3g palladium on charcoal under a pressure of 10 bar for 20h.

30 After filtering off the catalyst, the mixture was poured into water and extracted by using acetic acid ethyl ester. Then the aqueous phase was treated with sodium hydroxide solution to obtain a basic phase and subsequently extracted by using methylene chloride. After drying and concentrating the thus-obtained residue was poured into acetic acid ethyl ester and etherial HCl was added to obtain the corresponding hydrochloride. Yield: 4.2g (50%).

By reducing the time of hydrogenation the following product can be obtained in an analogous way:

6-Amino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol

General method for the acylation of benzocycloheptenyl amines:

2.5 mmol of the respective benzocycloheptenyl amine were mixed with 550 mg triethyl
amine and 5 ml dioxane, then 2.5 mmol of carboxylic acid chloride was added and stirred
5 at room temperature over a period of 2h.

The resulting mixture was then poured onto an ice/HCl-mixture, the obtained precipitate
was extracted with acetic acid ethyl ester, dried with sodium sulfate and then concentrated.
The thus-obtained residue was fractionated by prep. HPLC.

10 The following compounds were obtained according to the above method:

EX 1: 4-Fluoro-N-(6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-benzamide

[M+H+] measured: 284

mp.: 165°C

15 The enantiomers were separated by prep. HPLC (Chiralpeak AD, elution agent n-
heptane:isopropanol 10:1):,

a) (-)-4-Fluoro-N-(6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-benzamide

R_f-value: 10.11

b) (+)-4-Fluoro-N-(6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-benzamide

20 R_f-value: 11.52

**EX 2: 4-Fluoro-N-(5-hydroxy-6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-
benzamide**

mp.: 156°C

EX 3: 4-Chloro-2-methyl-N-(6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-benzamide

[M+H+] measured: 314

5 R_f-value: 5.42 (95% H₂O (0,05%TFA) to 95% acetonitrile, 4min, 95% acetonitrile 1,5min, Merck Porospher 3μ, 2x55mm)

EX 4: 2-Chloro-4-fluoro-N-(6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-benzamide

[M+H+] measured: 318

10 R_f-value: 5.19 (chromatogr. conditions according ex 3)

EX 5: 4-Ethoxy-N-(6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-benzamide

[M+H+] measured: 310

R_f-value: 5.25 (chromatogr. conditions according ex 3)

15

EX 6: 2,4-Difluoro-N-(6,7,8,9-tetrahydro-5H-benzocyclohepten-6-yl)-benzamide

[M+H+] measured: 302

R_f-value: 5.30 (chromatogr. conditions according ex 3)

20

Measurement of activation of eNOS transcription

Activation of eNOS transcription was measured as described in detail in Li et al.
25 "Activation of protein kinase C alpha and/or epsilon enhances transcription of the human endothelial nitric oxide synthase gene", Mol. Pharmacol. 1998; 53: 630-637.
Briefly, a 3,5kB long fragment 5' of the starting codon of the eNOS gene was cloned, sequenced and cloned in firefly luciferase expression plasmids to monitor activation of the

eNOS promoter by reporter gene activity. A human endothelial cell line stable transfected and expressing this promoter-reporter construct was used for compound testing. Cells were incubated for 18h with compounds.

5 All compounds were dissolved before in sterile DMSO. A final concentration of 0.5% DMSO in complete medium was allowed. Induction of reporter gene expression in these cells was measured using a standard luciferase assay system (Promega, Cat. No E150) according to the manufacturer's instructions. Luciferase induction in cells incubated with compounds were compared to those incubated with solvent alone. The ratio of both 10 activities (transcription induction ratio, TIR) was plotted as a function of compound concentration. Typically, TIR values started at low concentrations at a ratio of 1, indicating no compound effect, and extended up to a maximum TIR value TIR(max) which indicates the increase of the eNOS transcription. EC₅₀ values of transcription induction ratios as a function of compound concentration were determined graphically.

15 The effect of compounds on eNOS-transcription was confirmed in a second assay based on eNOS protein detection. Primary human umbilical vein cord endothelial cells (HUVEC) were isolated and cultivated according to standard procedures. Confluent cells were incubated with compounds for 18h and the effect on eNOS protein expression determined by a quantitative Westernblotting procedure. After compounds incubation, HUVEC were 20 lysed in ice-cold lysis buffer containing 10mM Tris-HCl, pH 8.0, 1% SDS and protease inhibitors. The lysate was subjected to a standard denaturating polyacrylamid gel electropheresis and blotted to nitrocellulose membranes. Using a specific primary monoclonal antibody (Transduction Laboratories, UK) and alkaline phosphatase labelled 25 secondary antibody (Jackson Labs), a specific eNOS protein band was visualized and quantified based on a chemifluorescence detection method.

The results are shown in the table below.

Compound No:	EC-50 (μ M)	TIR(max)
1	0.02	3.3
1a	0.001	3.2
1b	6.0	2.9
2	6.0	2.2
3	<0.08	2.2
4	<0.08	2.8

C mpound No:	EC-50 (μ M)	TIR(max)
5	<0.08	3.0
6	<0.08	3.0

The effect of the compounds according to the invention can also be investigated in the following animal models. (Animal experiments are performed in accordance to the German animal protection law and to the guidelines for the use of experimental animals as given by 5 the Guide for the Care and Use of Laboratory Animals of the US National Institutes of Health.)

Animals and Treatment (Experiments A - C)

10 ApoE and eNOS deficient mice (C57BL/6J background, Jackson Laboratory, Bar Harbor, Me) are used. All animals are 10 – 12 weeks of age and weigh 22 to 28 g. Three days before surgery mice are divided into 4 groups (apoE control, n=10-12; apoE with test compounds, n=10-12; eNOS control, n=10-12; eNOS with test compounds, n=10-12) and receive either a standard rodent chow (containing 4 % fat and 0,001 % cholesterol; in the 15 following designated as placebo group) or a standard rodent chow + test compound (10 or 30 mg/kg/d p.o.).

A Anti-hypertensive effect in ApoE knockout mice

20 Blood-pressure is determined in conscious mice using a computerized tail-cuff system (Visitech Systems, Apex, Nc). After treatment of ApoE deficient mice and eNOS deficient mice with the test compounds the blood pressure is compared to the results obtained with a placebo treatment.

B Inhibition of neointima formation and atherogenesis (femoral artery cuff)

30 After 3 day treatment of ApoE deficient mice with the respective compound, (10mg/kg/d pressed in chow), animals are anesthetized with an intraperitoneal injection of pentobarbital (60 mg/kg) followed by an intramuscular injection of xylazin (2 mg/kg) and a cuff is placed around the femoral artery as described in Moroi et al. (J Clin Invest. 101:1225-32, 1998). Briefly, the left femoral artery is dissected. A non-occlusive 2,0 mm polyethylene cuff made of PE-50 tubing (inner diameter 0,56 mm, outer diameter 0,965 mm, Becton Dickinson, Mountain View, Ca) is placed around the artery and tied in place

with two 7-0 sutures. The right femoral artery is isolated from the surrounding tissues but a cuff is not placed. Treatment with the respective compound is continued for 14 days after surgery. Then the animals are sacrificed. The aorta are taken for determination of vascular eNOS expressions by quantitative western blotting. Both femoral arteries are harvested,
5 fixed in formalin and embedded in paraffin. 20 cross sections (10 μ m) are cut from the cuffed portion of the left femoral artery and from the corresponding segment of the right artery. Sections are subjected to standard hematoxylin and eosin staining. Morphometric analyses are performed using an image analysis computer program (LeicaQWin, Leica Imaging Systems, Cambridge, GB). For each cross section the area of the lumen, the
10 neointima and the media are determined. To this end, the neointima is defined as the area between the lumen and the internal elastic lamina and the media is defined as the area between the internal and the external elastic lamina. The ratio between the area of the neointima and the area of the media is expressed as the neointima/media ratio. The results obtained in the compound group are compared to those obtained in the placebo group.

15

C Prevention of atherosclerotic plaque formation in chronic treatment

ApoE deficient mice are treated for 16 weeks with the respective compound pressed in
20 chow and finally sacrificed. Aortas are removed from each mouse, fixed in formalin and embedded in paraffin. Plaque formation is measured via lipid lesions formation in the aortas (from aortic arch to diaphragm) and is analyzed by oil red O staining. For quantifying the effect of the respective compound on vascular eNOS expression the femoral arteries are used in this experiment. The results obtained in the compound group
25 are compared to those obtained in the placebo group.

D Improvement of coronary function in diseased ApoE deficient mice

Old Male wild-type C57BL/6J mice (Charles River Wiga GmbH, Sulzfeld), and apoE
30 deficient mice (C57BL/6J background, Jackson Laboratory, Bar Harbor, Me) 6 month of age and weighing 28 to 36 g are used in the experiments. Mice are divided into 3 groups (C57BL/6, n=8; apoE control, n=8; apoE with respective compound, n=8) and receive for 8 weeks either a standard rodent chow (containing 4 % fat and 0,001 % cholesterol) or a standard rodent chow + respective compound (30 mg/kg/d p.o.).

35 Mice are anesthetized with sodium pentobarbitone (100 mg/kg i.p.), and the hearts are rapidly excised and placed into ice-cold perfusion buffer. The aorta is cannulated and connected to a perfusion apparatus (HUGO SACHS ELECTRONICS, Freiburg, Germany)

which is started immediately at a constant perfusion pressure of 60 mm Hg. Hearts are perfused in a retrograde fashion with modified Krebs bicarbonate buffer, equilibrated with 95% O₂ and 5 % CO₂ and maintained at 37.5° C.

A beveled small tube (PE 50) is passed through a pulmonary vein into the left ventricle and pulled through the ventricular wall, anchored in the apex by a fluted end, and connected to a tip-micromanometer (Millar 1.4 French). The left atrium is cannulated through the same pulmonary vein and the heart switched to the working mode with a constant preload pressure of 10 mm Hg and an afterload pressure of 60 mm Hg. Aortic outflow and atrial inflow are continuously measured using ultrasonic flow probes (HSE/Transonic Systems Inc.). Coronary flow is calculated as the difference between atrial flow and aortic flow. All hemodynamic data are digitized at a sampling rate of 1000 Hz and recorded with a PC using spezialized software (HEM, Notocord).

Hearts are allowed to stabilize for 30 min. All functional hemodynamic data are measured during steady state, and during volume- and pressure loading.

Left ventricular function curves are constructed by varying pre-load pressure. For acquisition of preload curves, afterload is set at 60 mm Hg and preload is adjusted in 5 mm Hg steps over a range of 5 to 25 mm Hg. Hearts are allowed to stabilize at baseline conditions between pressure- and volume-loading.

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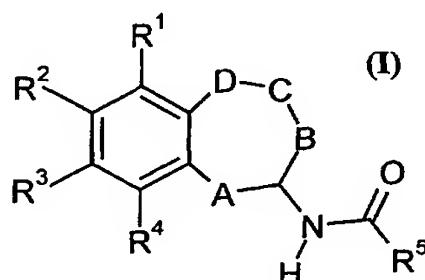
Aventis Pharma Deutschland GmbH

13. Februar 2001
APD61817EP IB/HN/AEW

Claims:

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1. An acylated 6,7,8,9-tetrahydro-5H-benzocycloheptenyl amine according to the general formula (I) or a pharmaceutically acceptable salt thereof



10

wherein

R¹ and R⁴ are independently from each other selected from the group consisting of: H; unsubstituted and at least monosubstituted C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl and C₂-C₁₀-alkynyl, the substituents of which are selected from the group consisting of F, OH, C₁-C₆-alkoxy, (C₁-C₆-alkyl)mercapto, CN, COOR⁶, CONR⁷R⁸, unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogens, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃; unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogens, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃; R⁹CO; CONR¹⁰R¹¹; COOR¹²; CF₃; halogenes; pseudohalogens; NR¹³R¹⁴; OR¹⁵; S(O)_mR¹⁶; SO₂NR¹⁷R¹⁸; and NO₂;

R² and R³ are independently from each other selected from the group consisting of: H; halogenes; pseudohalogens; unsubstituted and at least monosubstituted C₁-C₆-alkyl the substituents of which are selected from the group consisting of OH, phenyl, and heteroaryl; OH; C₁-C₆-alkoxy; phenoxy; S(O)_mR¹⁹; CF₃; CN; NO₂; (C₁-C₆-alkyl)amino; di(C₁-C₆-alkyl)amino; (C₁-C₆-alkyl)-CONH-; unsubstituted and at least monosubstituted phenyl-CONH- and phenyl-SO₂-O-, the substituents of which are selected from the group consisting of halogenes, pseudohalogens, CH₃ and methoxy; (C₁-C₆-alkyl)SO₂-O-; unsubstituted and at least monosubstituted (C₁-C₆-alkyl)CO, the substituents of which are selected from the group consisting of F, di(C₁-C₃-alkyl)amino, pyrrolidinyl and piperidinyl; and phenyl-CO, the phenyl part

of which can be substituted by one or more substituents from the group consisting of C₁-C₃-alkyl, halogenes and methoxy;

A is selected from the group consisting of CH₂, CHOH and CH-(C₁-C₃-alkyl);

5

B is selected from the group consisting of CH₂ and CH-(C₁-C₃-alkyl);

C independently has the same meaning as B;

10

D independently has the same meaning as B;

15

R⁵ is an aryl or a heteroaryl group which can be unsubstituted or carry one or more substituents selected from the group consisting of: halogenes; pseudohalogens; C₁-C₁₀-alkyl; C₃-C₅-alkandiyl; phenyl; phenylsubstituted C₁-C₄-alkyl; CF₃; OH; C₁-C₁₀-alkoxy; phenoxy; benzyloxy; CF₃O; (C₁-C₁₀-alkyl)COO; S(O)_mR²⁰; (C₁-C₁₀-alkyl)amino; di(C₁-C₁₀-alkyl)amino; (C₁-C₁₀-alkyl)-CONH-; (C₁-C₁₀-alkyl)-CON(C₁-C₃-alkyl)-; (C₁-C₁₀-alkyl)-CO; CF₃-CO; -OCH₂O-; -OCF₂O-; -OCH₂CH₂O-; -CH₂CH₂O-; phenylamino; phenyl-CO; COOR²¹; CONR²²R²³; SO₂NR²⁴R²⁵; and aromatic or aliphatic, mononuclear 5- to 7-membered heterocycles containing 1 to 3 heteroatoms from the group consisting of N, O and S which can be substituted by one or more substituents from the group consisting of halogenes, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃; wherein all phenyl groups and phenyl-containing groups which may be present in the said substituents of the said aryl or heteroaryl groups can be substituted by one or more groups selected from halogenes, pseudohalogens, C₁-C₃-alkyl, C₁-C₃-alkoxy, and CF₃;

20

25

R⁶ is H, C₁-C₆-alkyl or benzyl;

R⁷ is selected from the group consisting of:

30

H; C₁-C₆-alkyl which can be phenyl-substituted; phenyl; indanyl; and heteroaryl; and wherein each of the aforementioned aromatic groups can be unsubstituted or carry one or more substituents from the group consisting of halogenes, pseudohalogens, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃;

35

R⁸ is H or C₁-C₆-alkyl;

5 R⁹ is C₁-C₆-alkyl which can be unsubstituted or carry one or more substituents from the group consisting of: F; di(C₁-C₃-alkyl)amino; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of C₁-C₃-alkyl, C₁-C₃-alkoxy, halogenes, pseudohalogenes, and CF₃;

10 R¹⁰ independently has the same meaning as R⁷;

15 R¹¹ independently has the same meaning as R⁸;

20 R¹² independently has the same meaning as R⁶;

25 R¹³ is selected from the group consisting of: H; C₁-C₆-alkyl; and unsubstituted and substituted phenyl, benzyl, heteroaryl, phenyl-CO, and heteroaryl-CO, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C₁-C₃-alkyl, C₁-C₃-alkoxy, and CF₃, and wherein one or more of these substituents can be present;

30 R¹⁴ is H or C₁-C₆-alkyl;

35 R¹⁵ is selected from the group consisting of: H; C₁-C₆-alkyl; and substituted and unsubstituted benzyl, phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C₁-C₃-alkyl, C₁-C₃-alkoxy, and CF₃, and wherein one or more of these substituents can be present;

40 R¹⁶ is selected from the group consisting of: C₁-C₆-alkyl; CF₃; and substituted and unsubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C₁-C₃-alkyl, C₁-C₃-alkoxy, and CF₃, and wherein one or more of these substituents can be present;

45 R¹⁷ independently has the same meaning as R⁷;

50 R¹⁸ independently has the same meaning as R⁸;

55 R¹⁹ independently has the same meaning as R¹⁶;

60 R²⁰ independently has the same meaning as R¹⁶;

R²¹ independently has the same meaning as R⁶;

R²² independently has the same meaning as R⁷;

5

R²³ independently has the same meaning as R⁸;

R²⁴ independently has the same meaning as R⁷;

10

R²⁵ independently has the same meaning as R⁸;

heteroaryl is a 5 to 10-membered, mono- or bicyclic aromatic heterocycle containing one or more heteroatoms from the group consisting of N, O and S;

15

aryl is phenyl, naphth-1-yl or naphth-2-yl;

m is 0, 1 or 2.

2. An acylated 6,7,8,9-tetrahydro-5H-benzocycloheptenyl amine or a pharmaceutically acceptable salt thereof according to claim 1, wherein in the formula (I)

25

R¹ is selected from the group consisting of: H; C₁-C₄-alkyl; C₁-C₄-alkoxy; CF₃; halogenes; pseudohalogens; (C₁-C₄-alkyl)-S(O)_m-; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogens, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃, where heteroaryl is selected from the group consisting of 5- and 6- membered heterocycles containing one or more heteroatoms from the group consisting of N, O, and S;

30

R² is selected from the group consisting of: H; halogenes; pseudohalogens; and C₁-C₃-alkyl;

R³ and R⁴ are each H;

35

A is selected from the group consisting of CH₂ and CHOH;

B, C and D are independently from each other selected from the group consisting of CH₂ and CH-CH₃;

R⁵ is selected from the group consisting of: phenyl which is optionally substituted by one or more substituents from the group consisting of halogenes, pseudohalogenes, C₁-C₆-alkyl, CF₃, C₁-C₆-alkoxy, trifluoromethoxy, phenoxy, (C₁-C₃-alkyl)amino-, di(C₁-C₃-alkyl)amino, (C₁-C₄-alkyl)-S(O)_m-, phenylmercapto, phenyl which is optionally substituted by one or more halogenes, and -O-CH₂-O-, -O-CF₂-O-, and -OCH₂-CH₂-O-; unsubstituted and at least mono-halogene-substituted benzodioxolyl and dihydrobenzofuranyl; naphthyl which is optionally substituted by one or more substituents from the group consisting of halogenes, pseudohalogenes, C₁-C₆-alkyl, CF₃, C₁-C₆-alkoxy, trifluoromethoxy, phenoxy, (C₁-C₄-alkyl)-S(O)_m-, phenylmercapto, -O-CH₂-O-, -O-CF₂-O-, and -O-CH₂-CH₂-O-; and unsubstituted and at least monosubstituted heteroaryl the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C₁-C₆-alkyl, CF₃, C₁-C₆-alkoxy, trifluoromethoxy, phenoxy, (C₁-C₄-alkyl)-S(O)_m-, phenylmercapto, phenyl which is optionally substituted by one or more halogenes, and -O-CH₂-O-, -O-CF₂-O-, and -O-CH₂-CH₂-O-, where heteroaryl is selected from the group consisting of 5- to 10-membered mono- or bicyclic aromatic heterocycles containing one or more heteroatoms from the group consisting of N, O, and S;

m is 0 or 2.

3. An acylated 6,7,8,9-tetrahydro-5H-benzocycloheptenyl amine or a pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein in the formula (I)
25 R¹ is H, halogene or C₁-C₄-alkyl;

A, B and C are each CH₂;

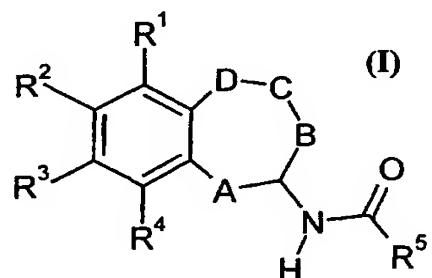
30 D is selected from the group consisting of CH₂ and CH-CH₃;

R⁵ is in particular selected from the group consisting of: 4-fluorophenyl; 4-chlorophenyl; 4-bromophenyl; 4-(C₁-C₃-alkyloxy)-phenyl; 4-trifluoromethoxyphenyl; 2-bromo-4-fluorophenyl; 2-chloro-4-fluorophenyl; 3,4-dimethylphenyl; 2,4-dimethylphenyl; 4-chloro-2-methylphenyl; 2-hydroxy-4-methylphenyl; 2-hydroxy-4-ethoxyphenyl; 2-methoxy-4-methylphenyl; 4-phenoxyphenyl; 3-fluoro-4-methylphenyl; benzo[1,3]dioxol-5-yl; 2,2-difluoro-

benzo[1,3]dioxol-5-yl; 2,3-dihydrobenzofuran-5-yl; thienyl; halogene-substituted thienyl; 5-acetylthienyl; pyridyl; pyridyl which is substituted by halogene and/or (C₁-C₃-alkyl);

5 heteroaryl is selected from the group consisting of furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, pyrazolyl, imidazolyl, pyrazinyl, pyridyl and pyrimidinyl.

10 4. An acylated 6,7,8,9-tetrahydro-5H-benzocycloheptenyl amine according to the general formula (I)



as defined in any of the claims 1 to 3,

15 or a pharmaceutically acceptable salt thereof,

for use as pharmaceutical.

20 5. The use of a compound as defined in any of claims 1 to 3 for the manufacture of a medicament for the stimulation of the expression of endothelial NO-synthase.

25 6. The use of a compound as defined in any of claims 1 to 3 for the manufacture a medicament for the treatment of cardiovascular diseases, stable and unstable angina pectoris, coronary heart disease, Prinzmetal angina, acute coronary syndrome, heart failure, myocardial infarction, stroke, thrombosis, peripheral artery occlusive disease, endothelial dysfunction, atherosclerosis, restenosis, endothel damage after PTCA, hypertension, essential hypertension, pulmonary hypertension, secondary hypertension, renovascular hypertension, chronic glomerulonephritis, erectile dysfunction, ventricular arrhythmia, diabetes and diabetes complications, nephropathy and retinopathy, angiogenesis, asthma bronchiale, chronic renal failure, 30 cirrhosis of the liver, osteoporosis, and restricted memory performance or a restricted

ability to learn, or the lowering of cardiovascular risk of postmenopausal women or after intake of contraceptiva.

7. A pharmaceutical preparation comprising an effective dose of at least one compound of the formula (I) as defined in any of claims 1 to 3 and/or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.
8. A pharmaceutical preparation according to claim 7, which pharmaceutical preparation is in the form of a pill, tablet, lacquered tablet, sugar-coated tablet, granule, hard or soft gelatin capsule, aqueous, alcoholic or oily solution, syrup, emulsion or suspension, suppository, solution for injection or infusion, ointment, tincture, spray or transdermal therapeutic systems, nasal spray, aerosol mixture, microcapsule, implant or rod.
9. A method for the synthesis of a compound according to the general formula (I) wherein R¹, R², R³, R⁴, R⁵, A, B, C and D have the meaning as defined in claim 1, which method comprises the coupling reaction of the respective 6,7,8,9-tetrahydro-5H-benzocycloheptenyl amine with an appropriate acid or acid chloride in the presence of an appropriate base and/or an appropriate coupling agent, optionally followed by a functionalization of the thus-obtained compound.

Aventis Pharma Deutschland GmbH

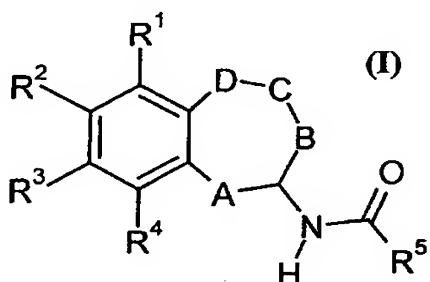
13. Februar 2001
APD61817EP IB/HN/AEW

Abstract

5

The present invention relates to acylated 6,7,8,9-tetrahydro-5H-benzocycloheptenyl amines according to the general formula (I) and their pharmaceutically acceptable salts, for use as pharmaceuticals.

10



The substituents R¹ to R⁵ and A, B, C and D have in particular the following meanings: R¹ is selected from the group consisting of: H; C₁-C₄-alkyl; C₁-C₄-alkoxy; CF₃; halogenes; 15 pseudohalogenes; (C₁-C₄-alkyl)-S(O)_m-; and unsubstituted and at least monosubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogenes, pseudohalogenes, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃, where heteroaryl is selected from the group consisting of 5- and 6- membered heterocycles containing one or 20 more heteroatoms from the group consisting of N, O, and S; R² is selected from the group consisting of: H; halogenes; pseudohalogenes; and C₁-C₃-alkyl; R³ and R⁴ are each H; A is selected from the group consisting of CH₂ and CHO_H; B, C and D are independently from each other selected from the group consisting of CH₂ and CH-CH₃; R⁵ is selected from the 25 group consisting of: phenyl which is optionally substituted by one or more substituents from the group consisting of halogenes, pseudohalogenes, C₁-C₆-alkyl, CF₃, C₁-C₆-alkoxy, trifluoromethoxy, phenoxy, (C₁-C₃-alkyl)amino-, di(C₁-C₃-alkyl)amino, (C₁-C₄-alkyl)-S(O)_m-, phenylmercapto, phenyl which is optionally substituted by one or more halogenes, and -O-CH₂-O-, -O-CF₂-O-, and -OCH₂-CH₂-O-; unsubstituted and at least mono-30 halogene-substituted benzodioxolyl and dihydrobenzofuranyl; naphthyl which is optionally substituted by one or more substituents from the group consisting of halogenes, pseudohalogenes, C₁-C₆-alkyl, CF₃, C₁-C₆-alkoxy, trifluoromethoxy, phenoxy, (C₁-C₄-alkyl)-S(O)_m-, phenylmercapto, -O-CH₂-O-, -O-CF₂-O-, and -O-CH₂-CH₂-O-; and unsubstituted and at least monosubstituted heteroaryl the substituents of which are selected

from the group consisting of halogenes, pseudohalogenes, C₁-C₆-alkyl, CF₃, C₁-C₆-alkoxy, trifluoromethoxy, phenoxy, (C₁-C₄-alkyl)-S(O)_m-, phenylmercapto, phenyl which is optionally substituted by one or more halogenes, and -O-CH₂-O-, -O-CF₂-O-, and -O-CH₂-CH₂-O-, where heteroaryl is selected from the group consisting of 5- to 10-
5 membered mono- or bicyclic aromatic heterocycles containing one or more heteroatoms from the group consisting of N, O, and S; m is 0 or 2.

The compounds are useful for the manufacture of medicaments for the treatment of cardiovascular diseases, stable and unstable angina pectoris, coronary heart disease,
10 Prinzmetal angina, acute coronary syndrome, heart failure, myocardial infarction, stroke, thrombosis, peripheral artery occlusive disease, endothelial dysfunction, atherosclerosis, restenosis, endothel damage after PTCA, hypertension, essential hypertension, pulmonary hypertension, secondary hypertension, renovascular hypertension, chronic glomerulonephritis, erectile dysfunction, ventricular arrhythmia, diabetes and diabetes
15 complications, nephropathy and retinopathy, angiogenesis, asthma bronchiale, chronic renal failure, cirrhosis of the liver, osteoporosis, and restricted memory performance or a restricted ability to learn, or the lowering of cardiovascular risk of postmenopausal women or after intake of contraceptiva.